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ABSTRACT

OBJECTIVES The aims of this study were to characterize the association of high-sensitivity cardiac troponin I (hs-cTnI) with heart failure (HF), to determine its predictive value beyond classical cardiovascular risk factors (CVRFs) and N-terminal pro–B-type natriuretic peptide, and to derive a relevant cutoff for potential clinical application.

BACKGROUND HF is an important contributor to the overall burden of cardiovascular disease. Early identification of individuals at risk could be beneficial for preventive therapies.

METHODS Based on the Biomarker for Cardiovascular Risk Assessment in Europe consortium, we analyzed individual-level data from 4 prospective population-based cohort studies including 48,455 individuals. Participants with myocardial infarction, HF, and stroke at baseline were excluded. We investigated the value of adding hs-cTnI to CVRFs and N-terminal pro–B-type natriuretic peptide using Cox proportional hazards survival models and for prediction by calculating C-statistics and Brier score.

RESULTS The median age of the study population was 51 years, and the median follow-up time for occurrence of HF was 6.61 years. Cox regression models adjusted for age, sex, and CVRFs revealed a significant association of hs-cTnI with incident HF (hazard ratio: 1.42 per log [ng/l] unit change [95% confidence interval: 1.31 to 1.53]). The best predictive value was achieved in the model with CVRFs (base model) and both biomarkers (C-index = 0.862; 95% confidence interval: 0.841 to 0.882). Optimal hs-cTnI cutoff values of 2.6 ng/l for women and 4.2 ng/l for men were derived for selecting individuals at risk.

CONCLUSIONS In this large dataset from the general population, hs-cTnI could show its independence for the prognosis of HF. (J Am Coll Cardiol HF 2020;8:401–11) © 2020 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

AIC = Akaike information criterion

BiomarCaRE = Biomarker for Cardiovascular Risk Assessment in Europe

eGFR = estimated glomerular filtration rate

hs-cTn = high sensitivity cardiac troponin

hs-cTnI = high-sensitivity cardiac troponin I

HR = hazard ratio

LDL = low-density lipoprotein

MI = myocardial infarction

NT-proBNP = N-terminal pro-B-type natriuretic peptide

Heart failure (HF) is one of the leading causes for morbidity and mortality in the Western population. The crude prevalence of HF is projected to increase by 25% over the next 20 years (1). Among middle-aged adults, the 10-year risk for new-onset HF is approximately 10% and even higher in older individuals (2). HF is diagnosed by its signs and symptoms, but imaging parameters are used to group patients in different HF subtypes based on ejection fraction (EF). Nevertheless, morbidity and mortality are similar for the different types (3). Treatment options for patients with reduced EF are improving, but in patients with only mildly reduced or preserved EF, no established therapy is available. This makes primary prevention of HF one of the unmet goals in HF research.

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A biomarker-driven diagnostic approach could potentially allow early identification of individuals at risk for developing HF. To date, established markers for risk prediction of incident HF are limited and seldom used in clinical practice.

N-terminal pro-B-type natriuretic peptide (NT-proBNP) is widely applied in the diagnosis and prognosis assessment of HF (4). A potential use in the context of the prediction of incident HF has also been demonstrated (5). Besides NT-proBNP, troponin is the most established cardiac biomarker and is used as the gold standard to detect myocardial injury (6,7). Novel high-sensitivity cardiac troponin (hs-cTn) assays may even allow application as a prognostic biomarker because very low concentrations can be detected (8). There is first evidence that even these low hs-cTn concentrations show a graded and independent association with incident HF (9–11). Also, Evans et al. (12) showed the association in their study. However, the pathophysiology as well as the prognostic implications of increased hs-cTn concentrations are not yet completely understood. Besides, cutoff values have not been uniformly defined and are always assay specific.

To examine the association of high-sensitivity cardiac troponin I (hs-cTnI) with HF in the general population, we conducted an analysis of prospective cohort studies within the BiomarCaRE (Biomarkers for Cardiovascular Risk Assessment in Europe) consortium. The aims of this study were to characterize the association of hs-cTnI with incident HF, to determine its predictive value beyond classical cardiovascular risk factors (CVRFs) and NT-proBNP, and to derive a relevant cutoff for potential clinical application.

METHODS

STUDY OVERVIEW. The BiomarCaRE consortium is a European Union–funded consortium including 31 institutions. BiomarCaRE aims to determine the value of established and emerging biomarkers to improve risk prediction of cardiovascular disease in Europe. BiomarCaRE relies on large-scale epidemiological cohorts with long-term follow-up based on the population of the MORGAM (MONICA Risk, Genetics, Archiving and Monograph) project as well as several cardiovascular disease cohorts and clinical trials. All epidemiological and clinical phenotypes as well as disease outcomes have been harmonized in a database (13).

STUDY COHORTS. Overall, the present analysis is based on the data of 4 population-based cohort studies from Denmark, Finland, Italy, and Sweden, in

(MIUR, Rome, Italy)-Programma Triennale di Ricerca, Decreto n.1588, and Instrumentation Laboratory, Milan, Italy. The Northern Sweden MONICA study was supported by Norrbotten and Västerbotten County Councils, the Swedish Research Council (2011_2395), the Swedish Research Council for Health, Working Life and Welfare, the Swedish Heart and Lung Foundation (20140799, 20120631, 20100635), and the Joint Committee of the County Councils in Northern Sweden. Dr. Blankenberg has received grants and personal fees from Abbott Diagnostics, Bayer, SIEMENS, and Thermo Fisher; grants from Singulex; and has received personal fees from AstraZeneca, AMGEN, Medtronic, Pfizer, Roche, Novartis, and SIEMENS Diagnostics outside the submitted work. Dr. Neumann has received personal fees from Abbott and Siemens; and has received grants from the German Heart Foundation/German Foundation of Heart Research and the Else Kröner Fresenius Stiftung outside the submitted work. Dr. Salomaa has received personal fees from Novo Nordisk; and has received grants from Bayer Ltd. outside the submitted work. Dr. Söderberg has participated in advisory boards for Actelion Ltd.; and has received speaker honoraria from Actelion Ltd. and Bayer Ltd. (unrelated to the present study). Dr. Kuulasmaa has received grants from the European Union and the Medical Research Council, during the conduct of the study. Dr. Westermann has received personal fees from Bayer, Boehringer Ingelheim, Berlin Chemie, AstraZeneca, Biotronik, and Novartis outside the submitted work. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC: Heart Failure* author instructions page.

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TABLE 1 Baseline Characteristics of the Study Population

	All (N = 48,455)	DanMONICA (n = 7,315)	FINRISK (n = 7,702)	Moli-sani (n = 23,179)	Northern Sweden MONICA (n = 10,259)
HF follow-up time, yrs	6.61 (6.55–6.66)	23.8 (18.8–27.4)	13.8 (13.8–13.9)	4.3 (3.4–5.3)	12.8 (7.8–20.9)
Age at baseline examination, yrs	50.7 (41.0, 60.7)	49.9 (39.8, 60.0)	47.1 (36.3, 58.1)	53.9 (45.5, 63.4)	47.8 (36.9, 58.7)
Men	23,321 (48.1)	3,662 (50.1)	3,758 (48.8)	10,943 (47.2)	4,958 (48.3)
Female	25,134 (51.9)	3,653 (49.9)	3,944 (51.2)	12,236 (52.8)	5,301 (51.7)
Cardiovascular risk factors					
Body mass index, kg/m^2	26.5 (23.7, 29.7)	24.3 (22.1, 27.1)	26.0 (23.4, 28.9)	27.4 (24.7, 30.7)	26.2 (23.5, 29.5)
Diabetes	2,208 (4.6)	157 (2.1)	366 (4.8)	1,367 (5.9)	318 (3.1)
Daily smokers	11,679 (24.2)	3,265 (44.6)	1,683 (22.2)	4,834 (20.9)	1,897 (18.6)
Hypertension	21,203 (43.8)	1,668 (22.8)	3,332 (43.3)	12,746 (55.0)	3,457 (33.7)
Systolic blood pressure, mm Hg	132.0 (119.5, 147.5)	121.0 (111.0, 134.0)	133.0 (121.0, 147.0)	138.0 (125.5, 153.0)	126.0 (115.0, 141.0)
LDL cholesterol, mmol/l	3.3 (2.6, 4.0)	3.6 (3.0, 4.4)	2.7 (2.1, 3.3)	3.2 (2.7, 3.8)	3.5 (2.7, 4.4)
HDL cholesterol, mmol/l	1.4 (1.2, 1.7)	1.4 (1.2, 1.7)	1.4 (1.1, 1.6)	1.4 (1.2, 1.7)	1.3 (1.1, 1.6)
Triglycerides, mmol/l	1.2 (0.9, 1.7)	1.1 (0.8, 1.6)	1.2 (0.9, 1.7)	1.2 (0.9, 1.7)	1.2 (0.9, 1.8)
Total cholesterol, mmol/l	5.6 (4.9, 6.4)	5.7 (5.0, 6.5)	5.4 (4.8, 6.2)	5.5 (4.8, 6.2)	5.8 (5.0, 6.7)
Antihypertensive medication	8,699 (18.2)	444 (6.3)	844 (11.3)	6,271 (27.2)	1,140 (11.3)
Biomarkers					
eGFR, ml/min/1.73 m^2	96.5 (85.1, 106.5)	98.9 (86.7, 109.8)	90.5 (78.2, 101.8)	94.8 (84.6, 103.3)	104.0 (92.8, 114.0)
hs-cTnI, ng/l	2.3 (1.4, 3.6)	2.8 (1.7, 4.2)	3.0 (2.0, 4.6)	2.2 (1.4, 3.3)	1.7 (0.9, 2.9)
NT-proBNP, ng/l	46.2 (24.5, 84.4)	-	44.7 (23.8, 80.8)	48.3 (25.8, 88.7)	42.0 (21.8, 78.5)
Outcome during follow-up					
Heart failure	1,990 (4.1)	609 (8.3)	485 (6.3)	508 (2.2)	388 (3.8)
Overall mortality	4,648 (9.6)	2,293 (31.3)	764 (9.9)	459 (2.0)	1,132 (11.0)

Values are median (95% confidence interval), or median (25th, 75th percentile), or n (%). Baseline characteristics for individuals free of heart failure, myocardial infarction and stroke at baseline. Results are shown for all studies combined. We classified subjects with systolic blood pressure over 140 mm Hg or diastolic blood pressure over 90 mmHg or taking antihypertensive medication as being hypertensive. Diabetes was defined as diagnosed, documented or self-reported.

LDL = low-density lipoprotein cholesterol; HDL = high-density lipoprotein cholesterol; eGFR = estimated glomerular filtration rate, CKD-EPI formula; hs-cTnI = high-sensitivity cardiac troponin I; NT-proBNP = N-terminal prohormone of brain natriuretic peptide.

particular DanMONICA, FINRISK, Moli-sani, and Northern Sweden MONICA, comprising 48,455 individuals with 1,990 events of incident HF. The initial aim of the participating studies was to monitor risk factor levels in the population, keeping in mind that such health examination surveys would also create a valuable baseline for cohort studies.

In DanMONICA, 7,315 individuals were enrolled from 1982 to 1992 for examination with a median follow-up time of 24.06 years. A total of 7,702 participants from FINRISK were admitted in 1997 for examination with a median follow-up time of 13.84 years. Northern Sweden enrolled 10,259 individuals from 1986 to 2009 for examination with a median follow-up time of 12.85 years. At last, Moli-sani enrolled 23,179 individuals from 2005 to 2010 for examination with a median follow-up time of 4.3 years. All individuals included in this study were free of cardiovascular disease containing HF, myocardial infarction (MI), and stroke. Each study cohort is based on a well-defined population (**Table 1**). Cohort descriptions are provided in the Supplemental Appendix. All participating cohort studies were approved by local ethics committees; individuals provided written informed consent.

DEFINITION OF THE ENDPOINT. Each study center was asked to decide on the exact definition of HF for their cohorts. When routine clinical and death certificate diagnoses are used, the relevant International Classification of Diseases codes are usually as follows: International Classification of Diseases-8th Revision, 427.0, 427.1, and 428; International Classification of Diseases-9th Revision, 428; and International Classification of Diseases-10th Revision, I50 (HF), I11.0 (hypertensive heart disease with HF), I13.0 (hypertensive heart and renal disease with HF), and I13.2 (hypertensive heart and renal disease with both HF and renal failure), which were adjusted according to local coding practices. In all cohorts, the follow-up for HF was based on linkage with hospital stay and cause of death registers and in FINRISK also with the national drug reimbursement register. The codes actually used, often based on national modifications of International Classification of Diseases-Eighth Revision and International Classification of Diseases-9th Revision, are specified in the MORGAM e-publication (14).

STATISTICAL METHODS. Missing data were handled by available case analyses; only those without missing

values on the variables involved in that particular analysis were used. Continuous variables are presented as median (25th and 75th percentile) and binary variables as absolute and relative frequencies.

Survival curves for HF were computed according to the following pre-selected categories derived from the continuous hs-cTnI: low, <1.9 ng/l whereas 1.9 ng/l was the reported limit of detection of the Abbott assay; moderate, 1.9 ≤3.2 ng/l; and high, >3.2 ng/l whereas 3.2 ng/l divides participants with a hs-cTnI ≥1.9 ng/l into 2 equal-sized subgroups, respectively (15).

To examine the association of hs-cTnI with HF, sex- and cohort-stratified Cox proportional hazards survival models with MI during follow-up as a time-dependent covariate were used. The use of sex and cohort as stratification variables adjusts the models for sex and cohort by allowing for a different baseline hazard function for each level combination of these 2 variables (16). Because individuals with MI at baseline were excluded, at the beginning of the follow-up time, the binary MI variable used in the Cox models was coded as 0 for all individuals, and it stayed this way until an individual experienced an MI. At that time, the variable value was updated to 1.

For these analyses, the Cox models were additionally adjusted in the first model for classical CVRFs, body mass index, systolic blood pressure, diabetes, smoking status, antihypertensive medication, low-density lipoprotein (LDL) cholesterol, and kidney function (estimated glomerular filtration rate [eGFR]). These variables were used as time fixed covariates because they were only available at baseline. Age was used as the time scale in all models. Body mass index, systolic blood pressure, LDL cholesterol, and eGFR were used as continuous variables. The reference category for diabetes is the absence of diabetes. The reference category for smoking is nonsmoking. The reference category for antihypertensive medication is the absence of antihypertensive medication.

In the first model, we added hs-cTnI to CVRFs. In the second model, we added hs-cTnI to CVRFs and NT-proBNP. Additionally, in the third model, we studied the association of NT-proBNP with HF after adjustment for CVRFs.

The association of hs-cTnI with HF was studied with the same setting of variables for continuous and categoric versions of hs-cTnI. The categorization of hs-cTnI is described earlier. The categoric variable of NT-proBNP was derived from the continuous version as well defined as low, <30.91 ng/l; moderate, ≥30.91 to <68.26 ng/l; and high, ≥68.26 ng/l. For these analyses, both biomarkers were log transformed and winsorized. Hs-cTnI and NT-proBNP values above the 99.5th percentile (106.6 ng/l and 1,356.2 ng/l, respectively) were winsorized.

The proportional hazard assumption was examined graphically and with formal tests using the methods described by Grambsch and Therneau (17). No evidence of violations of this assumption was observed. Hazard ratios for continuous versions of hs-cTnI or NT-proBNP were reported per log (ng/l) unit change.

To examine the prognostic value of hs-cTnI and NT-proBNP, the C-index (18), the Brier score (19), and calibration plots (20) were used beyond that from a model including CVRFs (defined as the base model in this analysis). Additionally, we used the Akaike information criterion (AIC) to estimate the relative quality of our statistical models (21).

One aim of this work was the determination of a clinically relevant cutoff value for hs-cTnI. This was done using the method of Contal and O'Quigley (22). This technique uses the log-rank test statistic in order to estimate the cutoff value. The optimal cutoff was chosen to give the maximum separation between the groups below and above the cutoff. The equality of survival curves defined by the optimal cutoff was tested using the methods described in the aforementioned reference.

A 2-sided p value <0.05 was considered statistically significant. All statistical analyses were conducted with R statistical software version 3.5.1 (23). Data collection and biomarker measurement as well as additional statistical information are detailed in the Supplemental Appendix.

STUDY OUTCOME. Of 51,190 individuals, prevalent HF, MI, and stroke cases (n = 2,735) were excluded from all analyses. There are 118 individuals with fatal MI and HF with tied event times. For these individuals, we assumed the event of HF to take place 1 day before death caused by MI. Under this assumption, these individuals could be included into the analysis. Additionally, there are 106 individuals who experienced nonfatal MI and HF at the same time. For these individuals, we assumed the event of nonfatal MI to take place 1 day before HF. The follow-up time of these 106 individuals ends at the time of experiencing MI. Sensitivity analyses underlying the reversed order of events for 106 individuals with tied event times provided similar conclusions.

RESULTS

BASELINE CHARACTERISTICS. Baseline characteristics for the overall study population and of each individual cohort are shown in **Table 1**. The median follow-up time for incident HF (95% confidence

TABLE 2 Performance Measures With C-Statistics, Brier Score, and Akaike Information Criterion

	C-Index (95% CI)	C-Index Difference to Base Model (95% CI)	p Value of C-Index	Brier Score	Akaike Information Criterion
Base model (CVRFs)	0.843 (0.822–0.863)			0.01553	12,081
Base model + hs-cTnI	0.848 (0.828–0.869)	0.005 (0.003–0.008)	<0.001	0.01545	11,998
Base model + NT-proBNP	0.861 (0.841–0.882)	0.018 (0.012–0.025)	<0.001	0.01511	11,790
Base model + NT-proBNP + hs-cTnI	0.862 (0.841–0.882)	0.019 (0.013–0.026)	<0.001	0.01509	11,774

CVRF variables were used to adjust the cause specific Cox models. Myocardial infarction was used as competing risk. If no biomarker was used in the model, these variables define the "base model." The base model includes body mass index, systolic blood pressure, smoker status, diabetes mellitus, antihypertensive medication, low-density lipoprotein, and kidney function. Models are stratified for cohort and sex. Age was used as the time scale of the Cox models (so they are implicitly adjusted for age). Five-yr event probabilities were used to compute C-indices, the Brier score, and the Akaike information criterion. The p value of C-index is shown against the base model.

CI = confidence interval; CVRF = cardiovascular risk factor.

interval [CI]) was 6.61 (6.55 to 6.66) years. A total of 1,990 (4.1%) participants developed HF, and 1,965 (4.1%) experienced MI. The overall mortality was 9.6% (n = 4,648). In the subgroup of individuals with incident HF, MI and overall mortality were considerably increased after the diagnosis of HF (MI = 29.4%, overall mortality = 45.4%). The median age was 50.7 years; 51.9% (n = 25,134) were women, and 48.1% were men (n = 23,321). The incident HF subgroup was older with a median age of 61.2 years and was composed of more male individuals (57.2%). The median body mass index was 26.5 kg/m^2; 43.8% were hypertensive, 4.6% were diagnosed with diabetes, and 24.2% were current smokers. The median LDL, high-density lipoprotein, and total cholesterol values were 3.3, 1.4, and 5.6 mmol/l, respectively. In the subgroup developing HF, all CVRFs including body mass index, systolic blood pressure, diabetes, smoking status, and blood lipids were more frequent (Supplemental Table 1). Missing information for individuals free of HF, MI, and stroke at baseline is shown in Supplemental Table 2.

DISTRIBUTION OF BIOMARKERS. A total of 46,065 measurements of hs-cTnI and 41,140 measurements of NT-proBNP were available. The distributions of these 2 biomarkers are skewed to the right.

The median concentrations of hs-cTnI and NT-proBNP were 2.3 ng/l and 46.2 ng/l, respectively (**Table 2**). The distribution of hs-cTnI with cutoff values for women and men and the reference value are shown in **Figure 1**. In the subgroup developing HF, baseline hs-cTnI was 4.0 ng/l, and NT-proBNP was 102.5 ng/l (Supplemental Table 1).

hs-cTnI AND ASSOCIATION WITH HF. As illustrated in the unadjusted Kaplan-Meier survival analyses across the categories of hs-cTnI levels, the probability of HF rose with increasing hs-cTnI levels for women and men (**Figure 2**).

Hazard ratios (HRs) for continuous hs-cTnI after the addition to model 1 consisting of CVRF variables were 1.42 (95% CI: 1.31 to 1.53; $p < 0.001$) and 1.19 (95% CI: 1.09 to 1.30; $p < 0.001$) after the addition to model 2 with CVRFs and NT-proBNP.

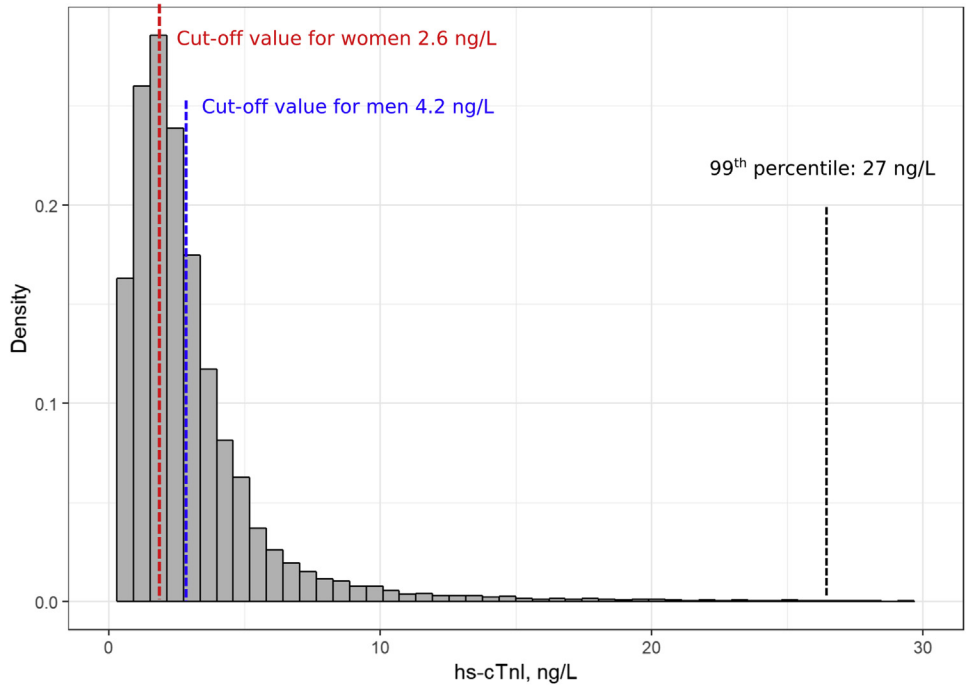
Figure 3 displays adjusted (model 2) HRs of HF for the categories of hs-cTnI and NT-proBNP using the lowest categories as reference. We observed the highest association for HF among those individuals with hs-cTnI levels above 3.2 ng/l with HR of 1.63 (95% CI: 1.32 to 2.03; $p < 0.001$) and among those with NT-proBNP levels above 68.26 ng/l with HR of 2.48 (95% CI: 2.02 to 3.03; $p < 0.001$). Cox proportional hazard ratios for traditional cardiovascular risk factors is shown in Supplemental Table 3. Results from combining the hs-cTnI and NT-proBNP categories and showing event rates of new-onset HF are presented in Supplemental Table 4.

hs-cTnI AND PREDICTION OF HF. The addition of hs-cTnI to the base model for the prediction of HF (C-index = 0.848; 95% CI: 0.828 to 0.869; Brier score = 0.01553) led to an increment in the C-index of 0.005 (95% CI: 0.003 to 0.008; $p < 0.001$). The addition of hs-cTnI and NT-proBNP to the base model yielded a C-index difference of 0.019 (95% CI: 0.013 to 0.026; $p < 0.001$) (**Table 1**). Further results of Brier score are also given in **Tables 1 and 3**, indicating the best results when adding both hs-cTnI and NT-proBNP to the base model. Additionally, when hs-cTnI was added to the base model, the AIC displayed a reduction from 12,081 (base model alone) to 11,998. The best predictive value with an AIC of 11,774 was found in the group with the base model, NT-proBNP and hs-cTnI (**Table 1**). The calibration plot is shown in Supplemental Figure 1.

CUTOFF VALUES OF hs-cTnI FOR POTENTIAL PREVENTIVE THERAPIES

After the application of the method used by Contal and O'Quigley (22), we calculated the cutoff value of hs-cTnI. To take into account possible sex-specific differences in hs-cTnI, we calculated 2 sex-specific

FIGURE 1 Distribution of hs-cTnI



The density (y-axis) of high-sensitivity cardiac troponin I (hs-cTnI levels) (x-axis) in the entire study population including 48,455 measurements. Dashed lines correspond to the cutoff value for women **(red)**, the cutoff value for men **(blue)**, and the 99th percentile of hs-cTnI in the healthy population **(black)**.

cutoff values: 2.6 ng/l for women and 4.2 ng/l for men. **Figure 4** shows the Kaplan-Meier curves for incident HF for 2 hs-cTnI categories divided by the cutoff values. In the follow-up time, participants in the category with hs-cTnI ≥2.6 (4.2) ng/l at baseline showed a significantly higher risk for incident HF compared with individuals with hs-cTnI under the cutoff values.

DISCUSSION

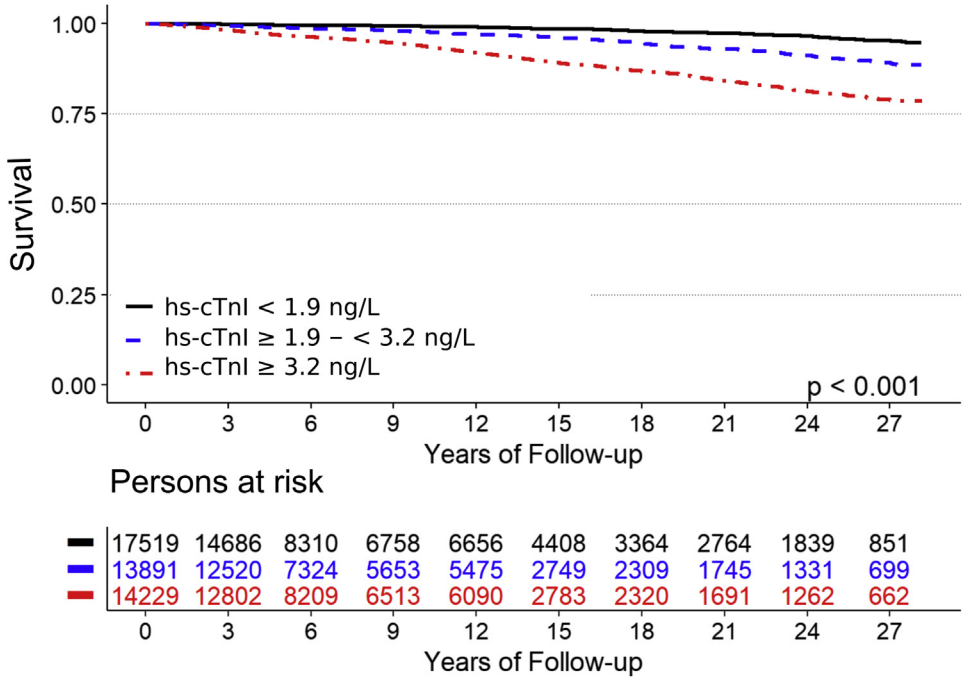
The main findings of this study based on harmonized data from large population-based cohorts are the following:

1. The 10-year event rate of HF with hs-cTnI (≥3.2 ng/l) and NT-proBNP (≥68.26 ng/l) was at 13.2%;
2. hs-cTnI levels were independently associated with incident HF;
3. The addition of hs-cTnI to a prognostic model consisting of CVRFs improved prediction of incident HF;
4. The best prediction value for incident HF was achieved by the combination of hs-cTnI and NT-proBNP into 1 model; and
5. Optimal hs-cTnI cutoff values of 2.6 ng/l for women and 4.2 ng/l for men were derived to select individuals at high risk (**Central Illustration**).

In the setting of pre-existing HF, scoring systems like the Meta-analysis Global Group in Chronic Heart Failure score (24) or the Seattle Heart Failure Model (10) have been developed to predict survival. A recent attempt to improve risk prediction by adding NT-proBNP has shown promising results (25). The addition of hs-cTnI to the established scoring systems may further improve prediction of HF and may allow tailored strategy for preventive therapies.

In this large population-based study, we focused on individuals with no prior history of HF to assess risk factors for possible prediction of incident HF. The rate of incident HF was about 4.1% in this population, and the median time to new-onset HF was 6.6 years. As expected, classical CVRFs could identify participants at risk to develop HF (**Figure 3**). Importantly, we show that hs-cTnI is associated with an increased incidence of HF in this large dataset and improved diagnostics on top of CVRFs. This is in agreement with earlier and smaller publications reporting an

FIGURE 2 Kaplan-Meier Curves According to Categories of hs-cTnI for the Endpoint HF



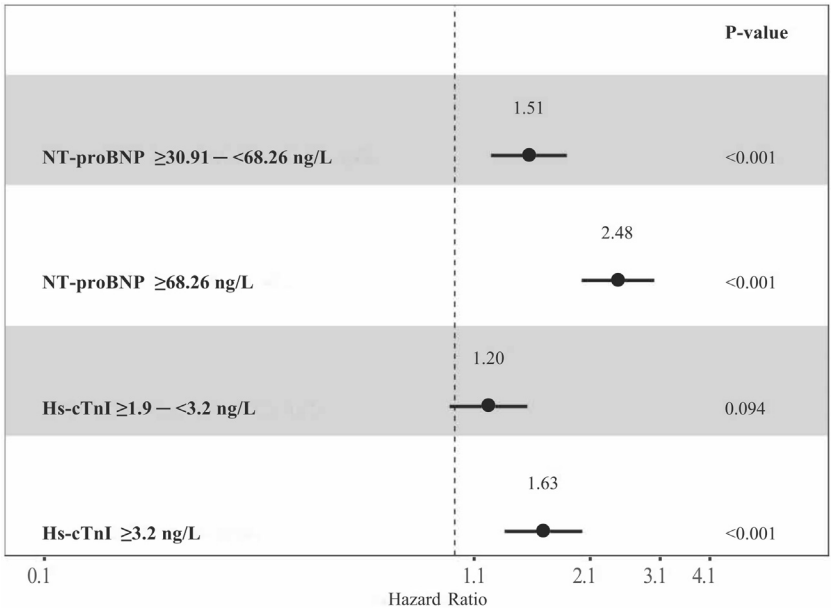
Survival curves divided in the categories hs-cTnI low: <1.9 ng/l, hs-cTnI moderate ≥1.9 ng/l to <3.2 ng/l, hs-cTnI high ≥3.2 ng/l. HF = heart failure; hs-cTnI = high-sensitivity cardiac troponin I.

independent association of hs-cTn to incident HF (9,26). Recently, Myhre et al. (27) showed an association of troponin T and diastolic function in a cohort of older adults.

Levels of hs-cTnI were low (**Figure 2**) as expected when compared with patients with acute MI. Nevertheless, also slight increases of hs-cTn have been shown to be important for risk predication in the general population (9) and are associated with a poor outcome. In our study, hs-cTnI concentrations of 2.6 ng/l for women and 4.2 ng/l for men predicted incident HF. Currently, uncertainty remains about the pathophysiology behind the hs-cTnI elevation. Seliger et al. (28) showed that hs-cTnT levels are associated with replacement fibrosis and progressive changes in left ventricular structure in cardiovascular disease-free adults using cardiac magnetic resonance. In this study, we excluded individuals with prevalent HF, MI, and stroke, which could have been responsible for a subtle increase of troponin. However, the long median time of more than 6 years until diagnosis of incident HF implies that most of those individuals were at good health at the time of inclusion and no clinical HF was present. The idea of troponin release in the nonacute setting is also discussed by the fourth definition of MI (29) with the inclusion of acute and chronic myocardial injury. Similar mechanisms might be responsible for the results in this study. Irrespective of the exact cause of troponin release, these patients would possibly benefit from therapeutic intervention. Our results suggest that hs-cTnI may help to identify those individuals.

The association between NT-proBNP and the incidence of HF is already established. In a randomized controlled trial, Huelsmann et al. (30) demonstrated the possibility of prevention of HF in persons with elevated NT-proBNP measurement. In this trial, individuals with elevated NT-proBNP underwent targeted prevention, resulting in a lower incidence of HF compared with the control groups. In accordance, the addition of NT-proBNP to a model containing classical CVRFs in our analyses improved risk prediction of HF. Nevertheless, similar to hs-cTnI, the detected values were low and could also be the result of subclinical myocardial injury causing this elevation. Furthermore, soluble suppression of tumorigenesis 2

FIGURE 3 Hazard Ratios for Incident HF According to Categories of NT-proBNP and hs-cTnI



A total of 48,455 individuals were admitted from 1982 to 2010 for examination. The 95% confidence interval of the median follow-up is 6.61 (6.55 to 6.66). Cox regression analysis for the endpoint HF after adjustment for cardiovascular risk factors (body mass index, systolic blood pressure, diabetes, smoking status, antihypertensive medication, low-density lipoprotein), kidney function (estimated glomerular filtration rate), and N-terminal pro-B-type natriuretic peptide (NT-proBNP) (in this analysis designed as model 2). The reference category for NT-proBNP was <30.91 ng/l. The reference category for hs-cTnI was <1.9 ng/l. Hazard ratios are reported per log (ng/l) unit change of hs-cTnI or NT-proBNP. **Black horizontal lines** map 95% confidence intervals. Abbreviations as in Figure 2.

also plays an important role in predicting HF (31). However, soluble suppression of tumorigenesis 2 measurement was not available in most of the cohorts and thus could not be included in our analysis.

Importantly, even when hs-cTnI was added to CVRFs and NT-proBNP, there was an improvement of prediction, albeit this was modest. Furthermore, this might be important for understanding the pathophysiology of the development of HF because next to stress-induced elevation explained by NT-proBNP, other mechanisms causing myocardial injury seem to play an important cause at this disease stage already.

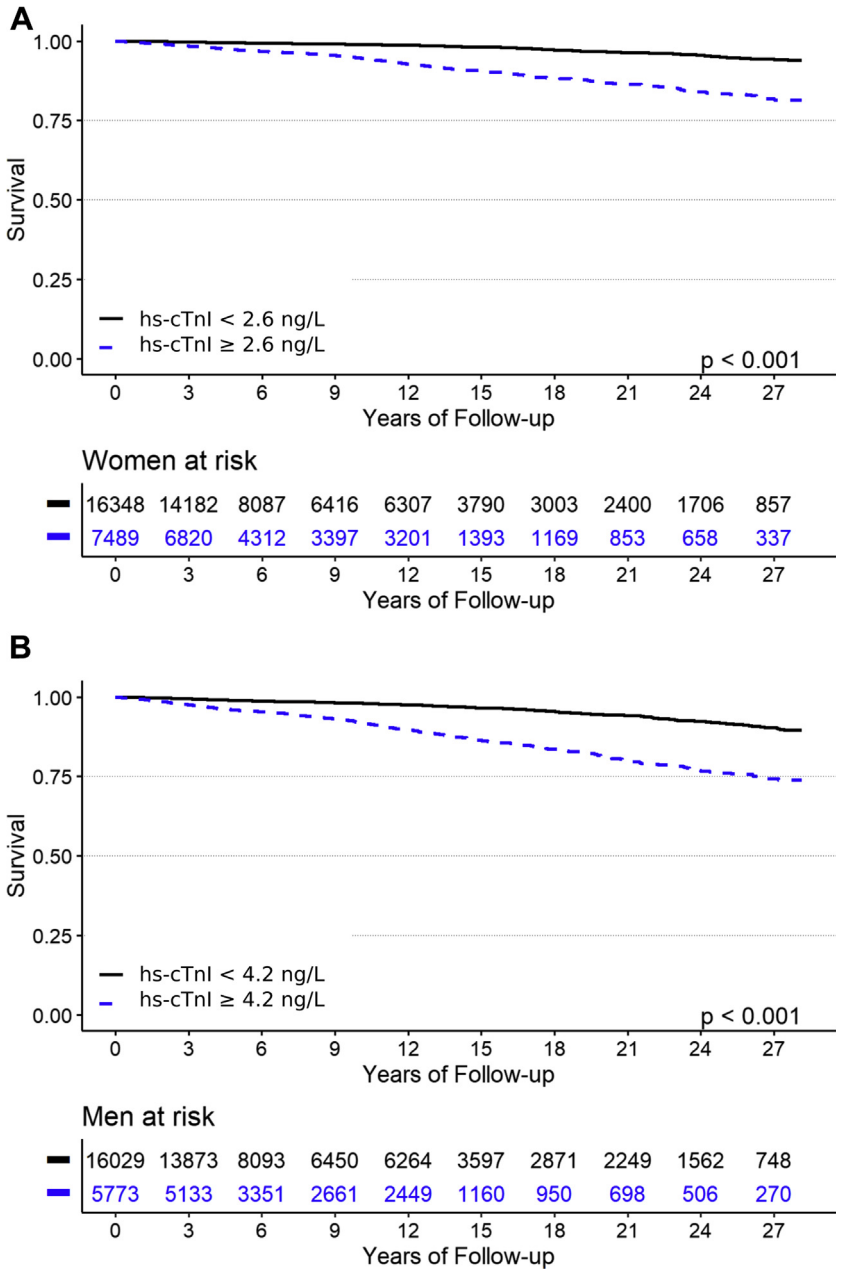
TABLE 3 Novel Findings: What Is New?

hs-cTnI levels were independently associated with incident heart failure (HF) with a hazard ratio of 1.42 in 48,455 individuals from the general population.
The addition of hs-cTnI to a prognostic model consisting of cardiovascular risk factors improved prediction of incident HF (C-index 0.848 vs. 0.843).
The best prediction value for incident HF was achieved by the combination of hs-cTnI and NT-proBNP with classical risk factors (C-index = 0.862).
10-yr event rates of HF differed relevantly between the lowest and highest hs-cTnI and NT-proBNP categories (0.6% vs. 13.2%).

High cardiac troponin levels were associated with future major adverse events including all-cause mortality, MI, readmission for HF, and stroke in other papers (9). Consequently, considering the high prevalence in the general population, developing reasonable therapeutic strategies for patients with elevated hs-cTnI levels in ambulatory primary care could be very important. Therefore, the hs-cTnI cutoff values of 2.6 ng/l for women and 4.2 ng/l for men beyond the CVRFs and NT-proBNP derived in this study may serve as a basis for future studies evaluating respective primary preventive strategies.

STUDY STRENGTHS AND LIMITATIONS. An important strength of our study is the considerable size of the dataset with harmonized data from well-defined European population cohorts with 48,455 participants examining explicitly hs-cTnI as a risk marker for HF. Several limitations have to be taken into

FIGURE 4 Kaplan-Meier Curves for Incident HF Based on the Calculated Cut-Off Value of hs-cTnI



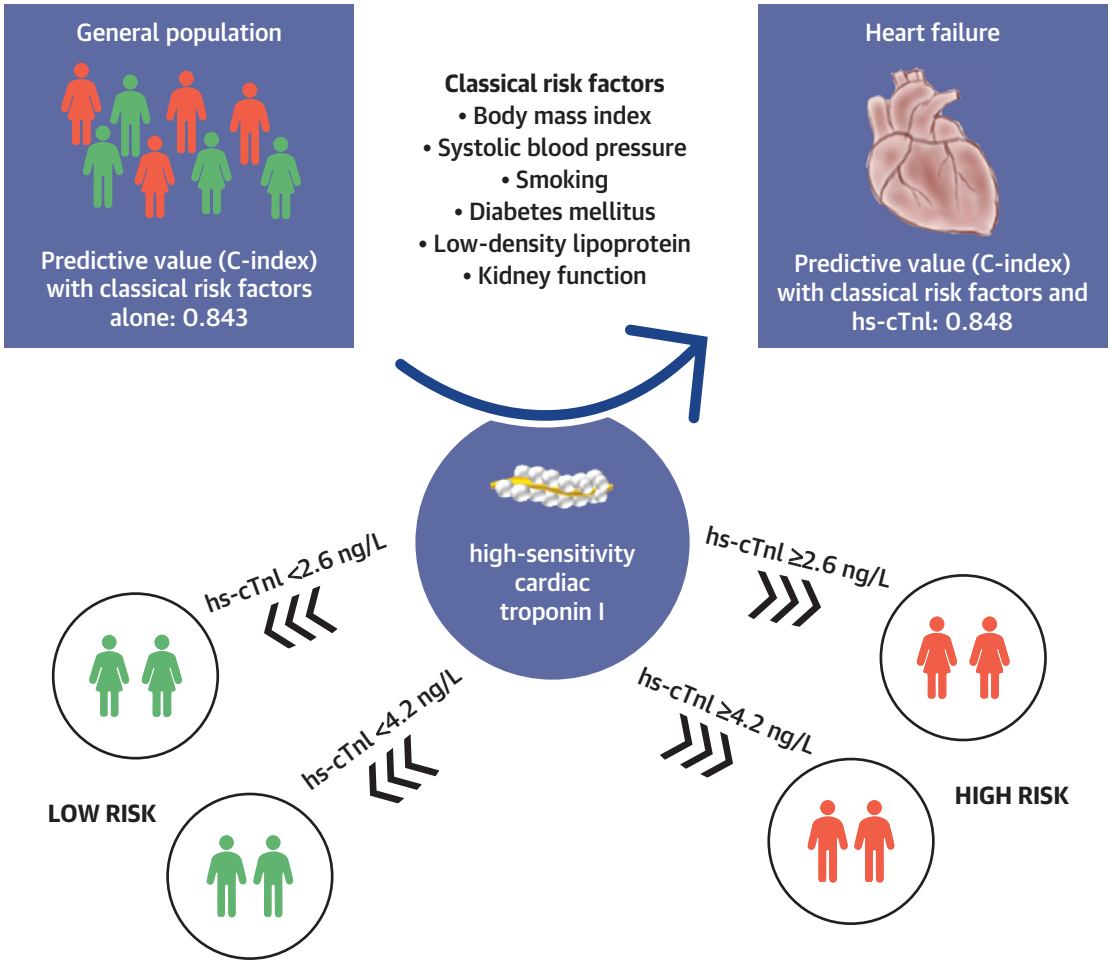
(A) Survival curves based on cut-off value for women hs-cTnI <2.6 ng/l and ≥2.6 ng/l. **(B)** Survival curves based on cut-off value for men hs-cTnI <4.2 ng/l and ≥4.2 ng/l. Abbreviations as in Figure 2.

account. One of the major limitations is that we cannot provide information on HF subtypes (HF with preserved and reduced ejection fraction) because these were not consistently collected in the included cohorts. Moreover, whether subclinical HF might have been present at enrollment cannot safely be ruled out in this population study. Another limitation is data on valvular heart disease, a possible risk factor for HF, are not available in our cohorts.

CONCLUSIONS

In this large dataset of population cohort, hs-cTnI as a biomarker could independently predict incident

CENTRAL ILLUSTRATION **Predictive Value of hs-TnI for HF in the General Population**



Yan, I. et al. J Am Coll Cardiol HF. 2020;8(5):401–11.

In this large dataset of healthy individuals, high-sensitivity cardiac troponin I (hs-cTnI) as a biomarker could show its independence for the prognosis of heart failure and predictive value in addition to classical risk factors. An optimal high-sensitivity cardiac troponin I (hs-cTnI) cutoff value of 2.6 ng/l for women and 4.2 ng/l for men was derived for selecting individuals who might benefit most from preventive strategies.

HF. The best prediction value for HF was achieved after hs-cTnI was combined with NT-proBNP. The usage of both biomarkers for the diagnosis of HF could be essential for future clinical decision making.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Elevation of serum hs-cTnI is associated with incident HF. hs-cTnI showed a marginal predictive value for HF.

TRANSLATIONAL OUTLOOK: Cutoff values of 2.6 ng/l for women and 4.2 ng/l for men were established. Further studies are needed to determine whether individuals with hs-cTnI > 2.6 ng/l/4.2 ng/l might benefit from specific preventive therapy.

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KEY WORDS BiomarCaRE, cardiovascular risk factors, high-sensitivity cardiac troponin I, N-terminal pro-B-type natriuretic peptide, prediction of heart failure

APPENDIX For a supplemental reference list, tables, and figures, please see the online version of this paper.